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Tanya A. Arenson
MEDLEN & CARROLL, LLP
Suite 350
101 Howard Street
San Francisco, CA 94105

EXAMINER	
GOLDBERG, JEANINE ANNE	
ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 04/12/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/699,941	BURMEISTER, MARGIT	
	Examiner	Art Unit	
	Jeanine A. Goldberg	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 February 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,4-12 and 15* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,4-12 and 15* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *2/2/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. This action is in response to the papers filed February 2, 2005. Currently, claims 1, 4-12, 15 are pending.

Election/Restrictions

2. Applicant's election without traverse of Group I, Claims 1, 4-12, 15 in the paper filed February 2, 2006 is acknowledged. Applicants further elected SEQ ID NO: 3.

Upon further consideration, since SEQ ID NO: 3 is the mRNA and SEQ ID NO: 11 is the genomic, the requirement to select a particular SEQ ID NO: has been withdrawn.

The requirement is still deemed proper and is therefore made FINAL.

This application contains subject matter drawn to polypeptides (see Claim 1) drawn to an invention nonelected without traverse in the paper filed February 2, 2006. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Priority

3. This application claims priority to provisional application 60/422,971, filed November 1, 2002 and 60/424,973, filed November 8, 2002.

Drawings

4. The drawings are acceptable.

Specification

5. The title of the invention is not descriptive of the elected invention. A new title is required that is clearly indicative of the invention to which the claims are directed.

Claim Rejections - 35 USC § 112-Description

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 1, 4-12, 15 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are broadly drawn to a method for detection of any variant Cayman ataxia nucleic acid by providing a sample from any subject and detecting the presence or absence of a variant in the sample.

Vas-Cath Inc. V. Mahurkar, 19 USPQ2b 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed". Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 USC 112 is severable from its enablement provision. In *The Regents of the University of California v. Eli Lilly* (43 USPQ2b 1398-1412), the court held that a generic statement which defines a genus of nucleic acids by only their functional activity does not provide an adequate written description of the genus. The court indicated that while Applicants are not required to disclose every species encompassed by a genus, the description of a genus is achieved by the recitation of a representative number of DNA molecules, usually defined by a nucleotide sequence, falling within the scope of the claimed genus. At section B(1), the court states that "An adequate written description of a DNA...' required a precise definition, such as by structure, formula, chemical name, or physical properties', not a mere wish or plan for obtaining the claimed chemical invention".

With respect to claims which encompass variants, as provided in Example 11, no common structural attributes identify the members of the genus. The current claims encompass a large genus of nucleic acids which comprise variants in any region of any Cayman ataxia nucleic acid. The genus includes an enormous number of variants,

polymorphisms and mutations for which no written description is provided in the specification. This large genus is represented in the specification by only the particularly named 2 polymorphisms for which data is provided. The specification teaches that "variants" refers to a gene or gene product that displays modifications in sequence and/or functional properties (altered characteristics) when compared to the wild-type gene (page 7, lines 15-20). This genus encompasses SNPs, deletions, insertions, translocations, microsatellites, for example.

The general knowledge and level of skill in the art do not supplement the omitted description because specific, not general guidance is what is needed. Since the disclosure fails to describe the common attributes or characteristics that identify members of the genus, and because the genus is highly variant, variants of Caymans ataxia gene alone is insufficient to describe the genus. There is no description of the mutational sites that exist in nature and there is no description of how the structure of Caymans ataxia gene relates to the structure of any strictly neutral alleles. The general knowledge in the art concerning variants does not provide any indication of how the structure of one allele is representative of unknown alleles. The nature of alleles is such that they are variant structures, and in the present state of the art the structure of one does not provide guidance to the structure of others. The common attributes are not described. The specification provides no correlation between structure of polymorphisms and the function of such polymorphisms. The polymorphisms shown are not representative of the genus of any polymorphism associated with Caymans ataxia because it is not clear which polymorphisms within the gene (coding or non-

coding) region of Cayman ataxia nucleic acid would have the same effect. One of skill in the art would conclude that applicant was not in possession of the claimed genus because a description of only one member of this genus is not representative of the variants of the genus and is insufficient to support the claim.

Accordingly, Applicants have not adequately disclosed the relevant identifying characteristics of a representative number of species within the claimed genus.

Claim Rejections - 35 USC § 112-Scope of Enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 1, 4-12, 15 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404,

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention and breadth of claims

The claims are broadly drawn to a method for detection of any variant Cayman ataxia nucleic acid by providing a sample from any subject and detecting the presence or absence of a variant in the sample.

The nature of the invention, therefore, requires the knowledge of predictive associations between any polymorphism in any Cayman ataxia nucleic acid and Caymans ataxia.

The invention is in a class of invention which the CAFC has characterized as "the unpredictable arts such as chemistry and biology." Mycogen Plant Sci., Inc. v. Monsanto Co., 243 F.3d 1316, 1330 (Fed. Cir. 2001).

The unpredictability of the art and the state of the prior art

The art teaches analysis of 19p13.3 region for markers which are associated with transmitted and non-transmitted chromosomes. Nystuen et al. (Human Mol. Genetics, Vol. 5, No. 4, pages 525-531, 1996) teaches analyzing a population from Cayman islands for genetic markers.

The art teaches genetic variations and associations are often irreproducible. Hirschhorn et al. (Genetics in Medicine. Vol. 4, No. 2, pages 45-61, March 2002) teaches that most reported associations are not robust. Of the 166 associations studied three or more times, only 6 have been consistently replicated. Hirschhorn *et al.* suggest a number of reasons for the irreproducibility of studies, suggesting population stratification, linkage disequilibrium, gene-gene or gene-environment interactions, and

weak genetic effects and lack of power are possible factors that lead to such irreproducibility. Hirschhorn *et al.* caution that the current irreproducibility of most association studies should raise a cautionary alarm when considering their use as diagnostics and prognostics (p. 60, Col. 2). Thus, Hirschhorn cautions in drawing conclusions from a single report of an association between a genetic variant and disease susceptibility.

Additionally, Ioannidis (Nature Genetics, Vol. 29, pages 306-309, November 2001) teaches that the results of the first study correlate only modestly with subsequent research on the same association (abstract). Ioannidis teaches that both bias and genuine population diversity might explain why early association studies tend to overestimate the disease protection or predisposition conferred by a genetic polymorphism (abstract).

The art teaches that presence of SNPs in the same gene does not indicate that each of the genes is associated with the same diseases. Meyer et al. (PG Pub 2003/0092019), for example, teaches that SNPs in the CADPKL gene are not each associated with neuropsychiatric disorders such as schizophrenia. Specifically Meyer teaches that cadpkl5 and cadpkl6 are not associated with the disease, however cadpkl7 has a p-value of less than 0.05, therefore an association exists. Each of these polymorphisms are SNPs within the CADPKL gene, however, it is apparent that they are not all associated in the same manner with disease. Thus, Meyer exemplifies that the association of a single SNP in a gene does not indicate that all SNPs within the gene are associated with the disease.

Guidance in the Specification and Working Examples

The specification provides no evidence that any variant in the Cayman ataxia nucleic acid is indicative of Caymans ataxia. The specification teaches that "variants" refers to a gene or gene product that displays modifications in sequence and/or functional properties (altered characteristics) when compared to the wild-type gene (page 7, lines 15-20). This genus encompasses SNPs, deletions, insertions, translocations, microsatellites, for example.

The specification teaches DNA from Cayman Ataxia patients, sequencing of exons and exon-intron boundaries identified two homozygous sequence variants: a G to C change in exon 9, predicting a serine to arginine substitution at amino acid 301, and a T to G substitution in the third base of intron 9. Both mutations completely segregated with the disorder/cannier status in over 40 family members that were genotyped blindly. None of over 1000 chromosomes from Caucasian, British, Jamaican, or African control samples showed either of the two mutations.

The guidance provided by the specification amounts to an invitation for the skilled artisan to try and follow the disclosed instructions to make and use the claimed invention.

Quantity of Experimentation

The quantity of experimentation in this area is extremely large since there is significant number of parameters which would have to be studied prior to using the claimed invention as broadly as claimed.

The claims recite a variant Cayman ataxia nucleic acid. However, the specification provides no express definition for what makes a sequence a "Cayman

ataxia nucleic acid". Cayman ataxia nucleic acid appears to encompass variants and homologs, which have not been taught or described by the specification. The specification only provides the sequence for a specific cDNA with SEQ ID NO: 3 and a specific genomic with SEQ ID NO: 11. The claims are further not limited to human patients and therefore encompass detection in any species, including any mammalian species such as mouse, dog, horse etc. The specification provides no teachings of Cayman ataxia for any other species, nor can they be found in the art at the time the invention was made, i.e. filed. Further the specification provides no gene sequence for any human Cayman genes, nor what the differences would be between a human gene vs that of another mammal. The nature of the invention require a predictable correlation between any polymorphism in any gene which fits within the broad scope encompassed by the claims and Caymans ataxia. The specification however only teaches two specific polymorphisms in relation to SEQ ID NO: 3 which is not commensurate in scope with the invention as broadly as it is claimed. It is not known whether this position exists in other variants or homologs or other mammalian genes or what a "corresponding" positions would be in another gene or whether a polymorphism would have the same effect in another gene.

The claims further recite a variant. The specification teaches that "variants" refers to a gene or gene product that displays modifications in sequence and/or functional properties (altered characteristics) when compared to the wild-type gene (page 7, lines 15-20). This genus encompasses SNPs, deletions, insertions, translocations, microsatellites, for example. It is unpredictable whether additional mutations, variants, insertions, deletions, SNPs, for example, are associated with Caymans ataxia. As provided in the art, associations between polymorphisms and disease are unpredictable. Not every mutation in a particular gene is associated with

disease. The skilled artisan would be unable to predictably correlate any other structural change in any other region of Cayman ataxia nucleic acid with Cayman ataxia. No common element or attributes of the sequences are disclosed which would permit selection of sequences as variants. No structural limitations or requirement which provide guidance on the identification of sequences which meet these functional limitations of associating a polymorphisms with Cayman ataxia is provided.

Furthermore, the claims are drawn to any subject including any animal such as dog, cat, monkey and mouse. The instant specification does not provide a Cayman ataxia nucleic acid for these subjects or species. It is unpredictable whether the polymorphisms from human are found within each of these species and whether these polymorphisms are associated with Caymans ataxia.

Finally, the claims are drawn to an association with ataxia, myoclonus, dystonia, epilepsy and nystagmus. The instant specification does not provide any association between these wide range of disorders. The specification analyzes Cayman Ataxia patients. It would be unpredictable and undue experimentation to analyze an association between each polymorphisms and each disorder where the art teaches associations are unpredictable. While the skilled artisan could test each polymorphism in an study with each disorder, the results of the experimentation are unpredictable and undue.

The quantity of experimentation in this area is extremely large as it requires analysis of each position in "any" Cayman ataxia nucleic acid to determine whether any alteration at each position is associated with Cayman ataxia. As neither the art nor the specification provide guidance as to which alterations as positions throughout Cayman ataxia are associated with Cayman ataxia, such analysis is replete with trial and error experimentation, with the outcome of each analysis being unpredictable. Screening

each possible alteration in any Cayman ataxia nucleic acid represents an inventive and unpredictable undertaking in itself, with many intervening steps, not provide any guarantee of success.

Level of Skill in the Art

The level of skill in the art is deemed to be high.

Conclusion

In the instant case, as discussed above, in a highly unpredictable art where the association of polymorphisms with diseases is not predictable, practice of the broadly claimed invention would be undue. Thus given the broad claims in an art whose nature is identified as unpredictable, the unpredictability of that art, the large quantity of research required to define these unpredictable variables, the lack of guidance provided in the specification, the absence of a working example and the negative teachings in the prior art balanced only against the high skill level in the art, it is the position of the examiner that it would require undue experimentation for one of skill in the art to perform the method of the claim as broadly written.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

8. Claims 1, 4, 6-12, 15 are rejected under 35 U.S.C. 102(b) as being anticipated by Nystuen et al. (Human Mol. Genetics, Vol. 5, No. 4, pages 525-531, 1996).

Nystuen teaches analysis of a Cayman Island population with ataxia which is characterized by psychomotor retaradation, cerebellar dysfunction, nystagmus, intention tremor, dysarthric speech and ataxic gait. Nystuen teaches a genome wide screen for short tandem repeat markers (abstract). As seen in Table 1, affected individuals had 100% D19S216 marker. Where parents and siblings contained much lower percentage of the markers. Moreover, Nystuen teaches that the D19S216 marker was found to be completely informative (heterozygous in all parents of affected individuals) and linked to the disease locus with no recombination. Moreover, Table 3 illustarates the transmission table showing the significant association between the disease bearing allele and the transmitted chromosome. Several markers illustrates are significantly associated with Cayman ataxia. The DNA samples were prepared from blood from human patients (limitations of Claim 9-12). The detection of the genotype was performed by amplification, electrophoresis (limitations of Claim 15).

Conclusion

9. No claims allowable.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Jeanine Goldberg whose telephone number is (571) 272-0743. The examiner can normally be reached Monday-Friday from 7:00 a.m. to 4:00 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla, can be reached on (571) 272-0735.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

The Central Fax Number for official correspondence is (571) 273-8300.

Jeanine Goldberg
Primary Examiner
April 10, 2006